REMARKS

Claims 1-9 are pending in the instant application. New claims 10 and 11 have been added. Accordingly, claims 1-11 will be pending in the application upon entry of the claims added herein.

Claims 10 and 11 have been added to claim more fully the instant invention. Support for the addition of claims 10 and 11 can be found in the specification and claims as originally filed. In particular, support can be found in the specification at least, for example, in working Examples 3, 5 and 6. No new matter has been added.

The claim additions made herein are solely for the purpose of expediting prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in this application. Applicants reserve the right to pursue the subject matter of claims as originally filed, or similar claims in this or one or more applications.

For the Examiner's convenience, the claims that will be pending upon entry of this amendment are also attached as Appendix A.

Claim Rejections

As a preliminary matter, Applicants gratefully acknowledge that the Examiner, in view of Applicants' previous amendments and remarks, has withdrawn the rejection under 35 U.S.C. §112, first paragraph, against claims 1-9.

Claim Rejections – 35 U.S.C. § 103

Rejection of Claims 1-7 Under 35 U.S.C. § 103(a)

The Examiner rejects claims 1-7 as being unpatentable over Marullo *et al.* (U.S. Patent No. 5,242,822; hereafter "Marullo") in view of the Dietzel *et al.* (*Cell* 50:1001-1010 (1987); hereafter "Dietzel"), Herskowitz et al. (Cell 50:995-9967 (1987); hereafter "Herskowitz"), and Whiteway *et al.,* (Cell 56:467-477 (1989); hereafter "Whiteway"). The Examiner states that Marullo and Dietzel "taken alone, provide all of the elements of the claimed invention." In particular, the Examiner relies on the Marullo for teaching "a yeast cell comprising a recombinant DNA encoding a heterologous G protein-coupled receptor." The Examiner relies on Dietzel for teaching "a yeast cell comprising a recombinant DNA encoding heterologous Gα subunit." The Examiner relies on Herskowitz and Whiteway for teaching in conjunction with Marullo and Dietzel "that G protein/G protein coupled receptor systems in yeast and mammals were known to be structurally and functionally analogous at the time the invention was made." In

combining the above references, the Examiner argues it would have been obvious for the skilled artisan to have arrived at the claimed invention. Applicants respectfully disagree.

Applicants' invention is directed to a transformed yeast cell comprising a heterologous G protein coupled receptor and a heterologous G protein that ***can operatively associate***, in a yeast cell ***incapable of expressing an endogenous G protein α -subunit***, and, for example, activate an endogenous yeast pheromone response (see, *e.g.*, claim 11). By contrast, neither of the foregoing references either alone or in combination teach or suggest such a cell.

Applicants respectfully disagree with the Examiner's conclusion that Marullo and Dietzel provide all the elements of the claimed invention as well as the interpretation of the results presented in Dietzel and conclusions drawn therefrom. Marullo is directed to the expression of receptors in cells for ligand binding assays without any regard to signal transduction. Thus, Marullo, fails to teach or suggest the claimed invention much less provide the requisite suggestion to combine its teachings with those of the Dietzel Herskowitz, and/or Whiteway.

Dietzel provides a cell expressing a rat Gα subunit gene which *partially* complements an *sst2* defect and *scg1* defect in yeast. The Examiner advises Applicants that "complete SCG1 complementation [is not] required in support of the instant rejection" because the "rejection is based upon the premise that a measurable biological response was produced in yeast cells by a heterologous rat Gα subunit when that subunit was activated by an endogenous, ligand activated G protein-coupled receptor." However, Applicants respectfully point out that Dietzel reports that the rat Gαs product is ***unable to operatively associate*** with the yeast pheromone receptor (*i.e.*, the endogenous yeast G protein-coupled receptor). For example, Dietzel states (at page 1007, second column, second full paragraph, last sentence) that (emphasis added):

> [t]he mating defect of the *scg1* mutants expressing rat Gαs suggests that this heterologous protein is ***not able to interact with activated a- or α-factor receptor [G protein-coupled receptor];*** therefore, GDP-GTP exchange would not occur in either [proposed] model [of signal transduction], resulting in an inability to activate the pheromone response pathway, leading to sterility.

The Examiner's citation from Dietzel noting that "the complementation of both the *sst2* and *scg1* defects by the rat α_s gene is striking" is not a teaching or suggestion that a heterologous G protein-coupled receptor and heterologous G protein can operatively associate. To the contrary, Dietzel clearly states that the complementation by the rat Gαs protein is "***due to the ability of this heterologous α subunit to interact with the effector***"

and that the rat G αs protein is "***not able to interact*** with activated a- or α-factor receptor [***G protein-coupled receptor***]" the effector and the receptor being two entirely different molecules (emphasis added; page 1007, col. 2, para. 2). Accordingly, Dietzel does not, as asserted by the Examiner, support the "premise that a measurable biological response was produced in yeast cells by a heterologous rat Gα subunit when that subunit ***was activated by*** an endogenous ligand activated ***G protein-coupled receptor***" because Dietzel expressly indicates that the rat Gα subunit did not operatively associate with the G protein coupled ***receptor***. Moreover, neither Marullo nor Dietzel teaches or suggests the operative association of a heterologous G protein coupled-receptor and heterologous G protein in a yeast cell ***incapable of expressing an endogenous G protein α-subunit***, as claimed.

Accordingly, Marullo and Dietzel, even in combination, fail to teach or suggest that a heterologous G protein coupled receptor and heterologous G protein can ***operatively associate, in the absence of an endogenous yeast G α subunit protein*** to, for example, produce an intracellular signal. Marullo fails to look at intracellular events and Dietzel teaches that a G protein coupled receptor and heterologous G protein ***do not operatively associate*** to produce an intracellular signal. The remaining references of Herskowitz and Whiteway do not make up for these deficiencies.

Indeed, Herskowitz calls into question whether a yeast G protein coupled receptor and yeast G protein operatively associate, stating (at page 996, col. 2; emphasis added) that the:

> identification of G protein involvement is less compelling, and though appealing, cannot be considered firm. There is at present ***no direct evidence for a physical or functional link between STE2 or STE3 proteins [i.e., yeast G protein coupled receptors] and the SCG1 (GPA1) gene product [i.e., a yeast G protein]***.

In view of these teachings, the skilled artisan would be discouraged from looking for an operative association between a G protein coupled receptor and corresponding G protein in the same organism much less an ***operative association*** between a heterologous G protein coupled receptor and a heterologous G protein as claimed, because Dietzel says they do not functionally interact and because Herskowitz also says there is no "physical or functional link" between such proteins. Thus, even in view of Whiteway, which allegedly teaches yeast homologs of mammalian Gβ and γ subunits (i.e., G proteins), the skilled artisan, in view of the above references, would not be motivated to look for an operative association between a heterologous G protein coupled receptor and heterologous Gα protein subunit as claimed.

As the Examiner is well aware, to establish a *prima facie* case of obviousness, there must first be some ***suggestion or motivation***, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a ***reasonable expectation of success*** at the time the invention was made. Finally, the combination must ***teach or suggest all the claim limitations***. See M.P.E.P. 2143.

Moreover, it is not sufficient that one of ordinary skill in the art could make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (Emphasis added)." *In re Dow Chemical Co.*, 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Regarding Marullo, this reference is directed to extracellular ligand binding to a receptor and is unconcerned with intracellular signal transduction events, for example, the operative association of a heterologous G protein coupled receptor and heterologous G protein. Thus, Marullo fails to ***provide any motivation*** to combine the reference with Dietzel, Herskowitz, and/or Whiteway references, because these references do not provide Marullo with any information that it does not already have or need. Accordingly, there is simply no motivation for Marullo to modify the references to arrive at the claimed invention.

In addition, the combination of Marullo, Dietzel, Herskowitz, and/or Whiteway references fails to provide any guidance whatsoever as to how to make a yeast cell comprising a heterologous G protein coupled receptor and a heterologous G protein α subunit which can operatively associate. Indeed, at least Dietzel and Herskowitz teach away suggesting that such proteins would not operatively associate, and thus suggest, that the claimed invention would be unlikely to work. Accordingly, ***the combination of references fail to provide any reasonable expectation of success*** in obtaining the claimed invention.

The Official Action, at page 3, second paragraph, indicates that " the Marullo et al. and Dietzel et al. references, take alone, provide all the elements of claimed invention. Marullo et al. provided a yeast cell comprising a recombinant DNA encoding a heterologous G protein coupled receptor and Dietzel et al. provided a yeast cell comprising a recombinant DNA encoding a heterologous Gα subunit." However, this statement is not accurate.

Applicants invite the Examiner's attention to the fact that the claimed invention includes two additional elements not taught or suggested by either of the references, alone or in combination; *i.e.*, (1) the heterologous G protein and heterologous Gα subunit operatively associate; and (2) the yeast cell is incapable of expressing an endogenous G protein α-subunit (yeast G_α). Because neither of these references teaches, alone or in combination, teaches or suggests these two elements, the references ***fail to teach each and every limitation of the claimed invention***, even if combined.

Accordingly, for at least these reasons, a *prima facie* case of obviousness has not been made out, and the claimed methods are inventive over the cited references. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1-7 under 35 U.S.C. §103(a).

Rejection of Claims 8-9 Under 35 U.S.C. §103(a)

Claims 8-9 are rejected as being unpatentable over the above references as applied to claims 1-7 and further in view of Nomoto et al. (EMBO 9:691-696 (1990); hereafter Nomoto). Specifically, the Examiner states that Nomoto discloses a "yeast cell line...containing a FUS1-lacZ fusion gene" and thus, in view of the above references, it would have been obvious to the skilled artisan to have "employed a yeast cell containing a mammalian G protein-coupled receptor and a compatible mammalian Gα subunit" thereby arriving at the claimed invention (i.e., claims 8 and 9). Applicants respectfully disagree.

As claims 8-9 depend from claims 1-7, Applicants assert that the arguments made above are equally applied here. In addition, Applicants submit that Nomoto does not make up for the deficiencies noted in Marullo, Dietzel, Herskowitz, and Whiteway because Nomoto does not suggest the use of a heterologous G protein coupled receptor and heterologous G protein that can operatively associate, much less in a yeast incapable of expressing an endogenous G protein α-subunit (yeast G_α), as claimed. To the contrary, Nomoto is entirely directed to the use of a FUS1-lacZ fusion gene in a yeast cell having ***only yeast components*** of the G protein coupled receptor pathway and ***not*** **a** ***heterologous*** G protein coupled receptor and ***heterologous*** G protein. Thus, for at least these reasons, claims 8-9 are inventive over the cited references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8-9 under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP

Peter C. Lauro, Esq.
Registration No. 32,360
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: **March 10, 2003**

Attachment: Appendix A

APPENDIX A

1. A transformed yeast cell containing a first heterologous DNA sequence which codes for a heterologous G protein coupled receptor and a second heterologous DNA sequence which codes for a heterologous G protein α subunit (G_α), wherein said first and second heterologous DNA sequences are capable of expression in said cell and can operatively associate, and wherein said cell is incapable of expressing an endogenous G protein α-subunit (yeast G_α).

2. A transformed yeast cell according to claim 1, wherein said first heterologous DNA sequence is carried by a plasmid.

3. A transformed yeast cell according to claim 1, wherein said second heterologous DNA sequence is carried by a plasmid.

4. A transformed yeast cell according to claim 1, wherein said heterologous G protein α subunit is selected from the group consisting of G_S α subunits, G_L α subunits, G_o α subunits, G_Z α subunits, and transducin α subunits.

5. A transformed yeast cell according to claim 1 which expresses a complex of the G protein β subunit and the G protein τ subunit ($G_{\beta\tau}$).

6. A transformed yeast cell according to claim 5 which expresses endogenous $G_{\beta\tau}$.

7. A transformed yeast cell according to claim 1, wherein said first heterologous DNA sequence codes for a heterologous G protein-coupled receptor selected from the group consisting of dopamine receptors, muscarinic cholinergic receptors, α-adrenergic receptors, β-adrenergic receptors, opiate receptors, cannabinoid receptors, and serotonin receptors.

8. A transformed yeast cell according to claim 1 further comprising a third heterologous DNA sequence, wherein said third heterologous DNA sequence comprises a pheromone-responsive promoter and an indicator gene positioned downstream from said pheromone-responsive promoter and operatively associated therewith.

9. A transformed yeast cell according to claim 8, wherein said pheromone responsive promoter is selected from the group consisting of the BAR1 gene promoter and the FUS1 gene promoter, and wherein said indicator gene is selected from the group consisting of the HIS3 gene and the LacZ gene.

10. (New) A transformed yeast cell according to claim 1, wherein said heterologous G protein coupled receptor and said heterologous G protein α subunit operatively associate and activate an endogenous yeast signal transduction pathway.

11. (New) A transformed yeast cell according to claim 10, wherein said endogenous yeast signal transduction pathway is a yeast pheromone response pathway.